

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SAL-PB60570	FOR FURTHER ACTION <small>see Form PCT/ISA/220 as well as, where applicable, item 5 below.</small>	
International application No. PCT/EP2004/012965	International filing date (day/month/year) 15/11/2004	(Earliest) Priority Date (day/month/year) 17/11/2003
Applicant SMITHKLINE BEECHAM CORPORATION		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box II).

3. ☐ **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

SUBSTITUTED PYRAZOLES AS PPAR AGONISTS

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

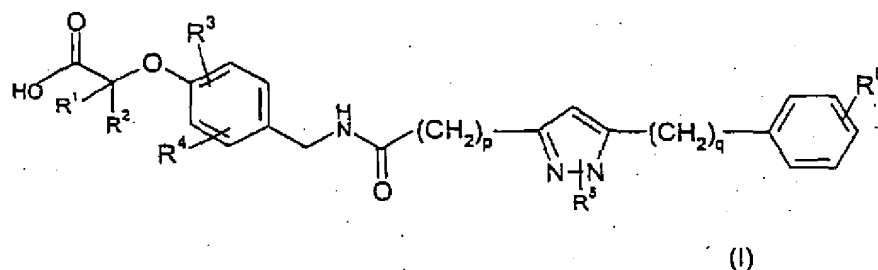
☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

A compound of formula (I) and pharmaceutically acceptable salts, solvates and hydrolysable esters thereof



wherein:

p is 0 or 1;

q is 0 or 1;

R¹ and R² are independently H or C₁₋₃ alkyl;

R³ and R⁴ are independently H, C₁₋₆ alkyl, -OC₁₋₆ alkyl, halogen, OH, C₂₋₆ alkenyl or CF₃;

R⁵ is H, C₁₋₆ alkyl (optionally substituted by one or more halogens, -COPhenyl, OC₁₋₆ alkyl, phenyl morpholino or C₂₋₆ alkenyl).

R⁶ is C₁₋₆ alkyl, halogen, -OCH₂ phenyl, phenyl (optionally substituted by C₁₋₃ alkyl), morpholino, pyrrolidino, piperidino, thiophenyl, furanyl pyridinyl or -OC₂₋₆ alkenyl.

These compounds activate the alpha and gamma subtypes of the hppar receptor and are useful e.g. in the treatment of diabetes, dyslipidemia or syndrome X.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP2004/012965

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/14 C07D409/10 C07D405/10 C07D401/10 C07D231/12
 A61K31/415 A61P3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/40207 A (GLAXO GROUP LIMITED; SIERRA, MICHAEL, LAWRENCE) 7 June 2001 (2001-06-07) cited in the application claims; examples	1-27
A	US 6 528 525 B1 (YANAGISAWA HIROAKI ET AL) 4 March 2003 (2003-03-04) table 1; compounds 1-62 table 2; compounds 2-84	1-27
A	WO 97/31907 A (GLAXO GROUP LIMITED; WILLSON, TIMOTHY, MARK; MOOK, ROBERT, ANTHONY, JR) 4 September 1997 (1997-09-04) cited in the application claims examples 25,61,63	1-27

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

2 March 2005

Date of mailing of the international search report

18/03/2005

Name and mailing address of the ISA

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Authorized officer

Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/012965

Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26,27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/012965

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0140207	A	07-06-2001	AT 265442 T	15-05-2004
			AU 758758 B2	27-03-2003
			AU 2003001 A	12-06-2001
			BR 0016067 A	06-08-2002
			CA 2393190 A1	07-06-2001
			CN 1402716 A	12-03-2003
			CZ 20021903 A3	15-01-2003
			DE 60010333 D1	03-06-2004
			DK 1244642 T3	16-08-2004
			WO 0140207 A1	07-06-2001
			EP 1244642 A1	02-10-2002
			ES 2219423 T3	01-12-2004
			HK 1047435 A1	26-11-2004
			HU 0203532 A2	28-02-2003
			JP 2003515597 T	07-05-2003
			MX PA02005456 A	29-11-2002
			NO 20022467 A	26-07-2002
			PL 356772 A1	12-07-2004
			PT 1244642 T	30-09-2004
			SI 1244642 T1	31-12-2004
			TR 200201473 T2	23-09-2002
			TR 200401772 T4	21-09-2004
			TW 555753 B	01-10-2003
			US 6518290 B1	11-02-2003
			ZA 200204241 A	02-07-2003
US 6528525	B1	04-03-2003	AU 738134 B2	06-09-2001
			AU 9279898 A	27-04-1999
			BR 9813019 A	05-09-2000
			CA 2305808 A1	15-04-1999
			CN 1280561 A	17-01-2001
			EP 1026149 A1	09-08-2000
			HU 0003881 A2	29-01-2001
			ID 24376 A	13-07-2000
			WO 9918066 A1	15-04-1999
			NO 20001689 A	31-05-2000
			NZ 503712 A	25-07-2003
			PL 339660 A1	02-01-2001
			RU 2176999 C2	20-12-2001
			TR 200000896 T2	21-09-2000
			US 2004006141 A1	08-01-2004
WO 9731907	A	04-09-1997	AP 780 A	22-11-1999
			AT 205485 T	15-09-2001
			AU 717699 B2	30-03-2000
			AU 2093597 A	16-09-1997
			BG 102792 A	31-08-1999
			BR 9707786 A	27-07-1999
			CA 2247443 A1	04-09-1997
			CN 1218460 A ,C	02-06-1999
			CY 2319 A	14-11-2003
			CZ 9802750 A3	13-01-1999
			DE 69706658 D1	18-10-2001
			DE 69706658 T2	20-06-2002
			DK 888317 T3	21-01-2002
			EA 1403 B1	26-02-2001
			EE 9800288 A	15-02-1999
			WO 9731907 A1	04-09-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/012965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9731907	A	EP 0888317 A1	07-01-1999
		ES 2163125 T3	16-01-2002
		HK 1015369 A1	15-02-2002
		HR 970110 A1	30-04-1998
		HU 0004845 A2	28-05-2001
		ID 15985 A	21-08-1997
		IL 125796 A	14-06-2001
		JP 3255930 B2	12-02-2002
		JP 2000507216 T	13-06-2000
		NO 983940 A	27-10-1998
		NZ 331381 A	23-06-2000
		OA 10843 A	14-08-2001
		PL 328871 A1	01-03-1999
		PT 888317 T	28-03-2002
		SI 888317 T1	30-04-2002
		SK 116398 A3	13-04-1999
		TR 9801707 T2	21-12-1998
		US 6294580 B1	25-09-2001
		ZA 9701645 A	10-12-1997

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/012965

International filing date (day/month/year)
15.11.2004

Priority date (day/month/year)
17.11.2003

International Patent Classification (IPC) or both national classification and IPC
C07D231/14, C07D409/10, C07D405/10, C07D401/10, C07D231/12, A61K31/415, A61P3/00

Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/012965

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/012965

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 26,27

because:

- ☒ the said international application, or the said claims Nos. 26,27 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/012965

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-27
	No: Claims	
Inventive step (IS)	Yes: Claims	1-27
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-25
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 26,27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the art:

The following documents have been cited:

- D1: WO 01/40207 A (GLAXO GROUP LIMITED; SIERRA, MICHAEL, LAWRENCE) 7 June 2001 (2001-06-07)
- D2: US-B1-6 528 525 (YANAGISAWA HIROAKI ET AL) 4 March 2003 (2003-03-04)
- D3: WO 97/31907 A (GLAXO GROUP LIMITED; WILLSON, TIMOTHY, MARK; MOOK, ROBERT, ANTHONY, JR) 4 September 1997 (1997-09-04)

V-2. Novelty (Art. 33(2) PCT):

The claims differ from D1 in the pyrazole moiety (D1 discloses oxazoles and thiazoles). The pyrazoles of D2 and D3 do not have the same substitution pattern and are no amides (cf. e. g. examples 1-62 and 2-84 of D2; examples 25, 61, 63 of D3).

V-3. Inventive Step (Art. 33(3) PCT):

Closest prior art is seen in D1. The compounds disclosed in D1 are ppar modulators.

The problem to be solved is the provision of further ppar modulators. The difference of the present claims with respect to D1 lies in the replacement of the oxazole/thiazole moiety of D1 by pyrazoles. This modification is not suggested by the prior art since the pyrazoles of D2 and D3 do not disclose the 3,5-substitution pattern (cf. above) in similar molecules and thus the equivalence was not obvious.

Art. 33(3) PCT is thus fulfilled for the present claims.